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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. |
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| 09/148,234 | 09/04/98 | MOUTSATSOS I | GI5298A |

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| **ART UNIT** | **PAPER NUMBER** |
| 1636 | 13 |

**DATE MAILED:** 02/28/00

**Please find below and/or attached an Office communication concerning this application or proceeding.**

**Commissioner of Patents and Trademarks**

| Office Action Summary | Application No. 09/148,234 | Applicant(s) Moutsatos et al. |
|---|---|---|
| | Examiner WILLIAM SANDALS | Group Art Unit 1636 |

☒ Responsive to communication(s) filed on *Nov 18, 1999*.

☒ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

**Disposition of Claims**

☒ Claim(s) *11-23* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *11-23* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

**Application Papers**

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. § 119**

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

**Attachment(s)**

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

*--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---*

## DETAILED ACTION

### *Response to Arguments*

1. Applicant's arguments with respect to claims 1-10 have been considered but are moot in view of the new ground(s) of rejection. Cancellation of claims 1-10 and entry of new claims 11-23 which are drawn to new subject matter have necessitated new grounds of rejection and therefore **this rejection is made final**.

### *Specification*

2. The use of the trademarks RNAZOL, NONIDET, RNEASY, TRITON and DE-CAL have been noted in this application. They should be capitalized wherever they appear and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

### *Claim Rejections - 35 USC § 112*

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 11-23 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for cultured cells and bone marrow stromal cells, does not reasonably provide enablement for any progenitor cell. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The claims are drawn to a method of producing progenitor cells for implantation at the site of a bone infirmity in a human. While applicants have shown a method of producing cultured or bone marrow stromal cells for implantation at the site of a bone infirmity in a rodent, they have not demonstrated any method for producing **any** progenitor cells other than cultured cells and bone marrow stromal cells for implantation at the site of a bone infirmity in a rodent. In order to do so, undue experimentation is required. Whether undue experimentation is needed is not based on a single factor, but rather a conclusion reached by weighing many factors. Many of these factors have been summarized in *In re Wands*, 858 F.2d 731, USPQ2d 1400 (Fed. Cir. 1988).

The Wands factors as they apply to the instant claimed invention are as follows:

a- The quantity of experimentation necessary to reduce the instant claimed invention to practice would involve the demonstration of the suitability of any other type of cell for practicing the instant claimed method.

b- Only examples of cultured cells and bone marrow stromal cells have been presented and only limited prophetic guidance has been presented on the use of any other type of progenitor cell.

c- The nature of the invention is complex. Gene therapy, the introduction of recombinant DNA into cells, is a new and developing art and the use of pluripotent cells is poorly understood in the area of gene therapy.

d- The prior art taught by Orkin et al. (see especially the section on "Gene transfer and expression" and "Gene therapy in man status of the field") described many problems in the developing field of gene therapy. Recited problems include: lack of efficacy, adverse short term effects and limited clinical experience, the inability to extrapolate experimental results and unreliability of animal models. Problems with the vector include: host immune response to the vector and the expressed product, difficulty of targeting the vector to the desired site, transient expression of the gene of interest and low efficiency of delivery of the vector to the targeted site.

e- Marazzi et al. (see especially the abstract and the introduction) describe attempts to use embryonic stem cells (which are pluripotent cells) with a bone morphogenetic protein (BMP-4) which resulted in the cell death of the embryonic stem cells. The results of Marazzi et al. show the unpredictability of the use of pluripotent cells in practicing the newly developing art of gene therapy.

g- Therefore, given the analysis above, it must be considered that the skilled artisan would have needed to have practiced considerable non-routine, trial and error experimentation to enable the full scope of the claims.

Therefore, given the analysis above, it must be considered that the skilled artisan would have needed to have practiced considerable non-routine, trial and error experimentation to enable the full scope of the claims.

***Claim Rejections - 35 USC § 103***

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 11-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat No. 5,763,416 or WO 96/39431 in view of US Pat No. 5,645,084 and US Pat No. 5,700,774.

US Pat No. 5,763,416 taught (see especially columns 3-5 and 7-12) or WO 96/39431 taught (see especially pages 2, 15-16, 19, 33 and the claims) a method of producing cultured or bone marrow stromal cells for implantation at the site of a bone infirmity by transfecting the cells with recombinant bone morphogenic protein. US Pat No. 5,763,416 at column 3 suggests the use of PTH in the method, where BMP and PTH can be coexpressed in the target cells, and identifies the requirement of BMP and/or PTH receptors in the target cells. US Pat No. 5,763,416 at

column 4 suggests the use of bone progenitor cells. WO 96/39431 taught that the bone morphogenic protein was BMP-10. US Pat No. 5,763,416 taught that the method may be practiced with BMP-2 as well as other bone morphogenetic proteins.

US Pat No. 5,763,416 did not teach that the cells coexpress PTH and a PTH receptor. WO 96/39431 did not teach that the BMP was BMP-2, nor that the cells were progenitor cells, nor that the cells coexpress PTH and a PTH receptor.

US Pat No. 5,645,084 taught (see especially column 4) that BMP-2 is closely related to the BMP-10 of WO 96/39431, where BMP-2 and BMP-10 may be used interchangeably in a method of use for treating a bone infirmity.

US Pat No. 5,700,774 taught (see especially columns 1 and 2) the interchangeability of BMP-2 and BMP-10, as well as the use of PTH and PTH receptor in cells in need of treatment with BMP-2, where the affected bone-generating target cells are known to express PTH receptor.

It would have been obvious to one of ordinary skill in the art at the time of filing of the instant specification to combine the method of producing cultured or bone marrow progenitor cells for implantation at the site of a bone infirmity by transfecting the cells with recombinant bone morphogenic protein of US Pat No. 5,645,084, or the method of producing cultured cells for implantation at the site of a bone infirmity by transfecting the cells with recombinant bone morphogenic protein of WO 96/39431 with the interchangeable BMP-2 protein of US Pat No. 5,645,084 or the interchangeable BMP-2 protein of US Pat No. 5,700,774 where PTH and PTH receptor are known to be produced in the target cells of the method because all of the references

taught the treatment of bone infirmities with BMP's, and the BMP's are shown to be interchangeable for the use of treating a bone infirmity, and PTH and PTH receptor are known to be expressed in the target cells.

One of ordinary skill in the art would have been motivated at the time of filing of the instant specification to combine the method of producing cultured or bone marrow progenitor cells for implantation at the site of a bone infirmity by transfecting the cells with recombinant bone morphogenic protein of US Pat No. 5,763,416, where US Pat No.5,763,416 recites at column 4, "this invention provides advantageous methods for using genes to stimulate bone progenitor cells" or the method of producing cultured cells for implantation at the site of a bone infirmity by transfecting the cells with recombinant bone morphogenic protein of WO 96/39431 which recites at page 19 "cells from a patient may be engineered with a polynucleotide (DNA or RNA) encoding a polypeptide *ex vivo*, with the engineered cells then being provided to a patient to be treated with the polypeptide", with the interchangeable BMP-2 protein of US Pat No. 5,645,084 or the interchangeable BMP-2 protein of US Pat No. 5,700,774 where PTH and PTH receptor are known to be produced in the target cells of the method where they state at column 2, lines 10-13 "said compositions comprising one or more protein members of the transforming growth factor-ß (TGF-ß) superfamily together with parathyroid hormone related peptide" because all of the references taught the treatment of bone infirmities with BMP's, and the BMP's are shown to be interchangeable for the use of treating a bone infirmity, and PTH is also useful to be used in conjunction with a member of the TGF-ß family (BMP-2), and that PTH receptor is

known to be expressed in the target cells. Further, a person of ordinary skill in the art would have had a reasonable expectation of success in the producing the instant claimed invention given the teachings of US Pat No. 5,763,416 or WO 96/39431 with US Pat No. 5,645,084 and US Pat No. 5,700,774.

***Conclusion***

7. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

8. Certain papers related to this application are ***welcomed*** to be submitted to Art Unit 1636 by facsimile transmission. The FAX numbers are (703) 308-4242 and 305-3014. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61

(November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant *does* submit a paper by FAX, the original copy should be retained by the applicant or applicant's representative, and the FAX receipt from your FAX machine is proof of delivery. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications should be directed to Dr. William Sandals whose telephone number is (703) 305-1982. The examiner normally can be reached Monday through Friday from 8:30 AM to 5:00 PM, EST. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. George Elliott can be reached at (703) 308-4003.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group Receptionist, whose telephone number is (703) 308-0196.

William Sandals, Ph.D.

Examiner

February 27, 2000

DAVID GUZO
PRIMARY EXAMINER